

# An Autopsy Study of Human Axillary Lymph Node Histology

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This is a histologic study of axillary lymph nodes removed from 487 random autopsies. Histologic features such as germinal centers, deep cortical regions, sinus histiocytosis, hyaline deposition, fibrosis and overall cellularity were evaluated in each case. Results were correlated with the age of the deceased and cause of death. The results a) support the general opinion that germinal centers are more frequently found in children and young adults than in the old, b) showed that hyaline deposits increase with age, c) showed that lymphocyte depletion associated with fibrosis and hyaline deposits was found in patients dying of chronic disease, particularly cancer, d) pointed out a selective depletion of the deep cortical regions in patients dying of hemorrhage, and e) contributed to knowledge of the morphology of axillary lymph nodes in neonates. (Am J Pathol 78:7-22, 1975)

LYMPH NODES constitute a substantial component of the immune system strategically located in various areas of the body. Lymph nodes serve as areas of antigen retention and a site of immunologic education and expansion of lymphocyte populations. They also represent a site where differentiation of plasma cells or immunoglobulin-secreting cells takes place, and they are thus major organs of antibody synthesis and secretion. Morphologic techniques in recent years have been instrumental in defining areas of the lymph node as being thymus dependent, taking active role in cell-mediated immune responses and others in which thymus-independent cells abound that participate in antibody-mediated cellular immunities and humoral immune responses.

In the course of studies on the morphology of lymph nodes in patients with cancer,<sup>1,2</sup> the authors, as have others,<sup>3</sup> realized that good descriptions of human lymph node morphology are relatively few. Much of the literature that is available dates back 40 years or more, when it was largely directed towards analysis of the meaning and function of sec-

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ondary nodule formation.<sup>4-8</sup> The morphology of human lymph nodes in different areas of the body and different age groups and the changes occurring in chronic diseases other than cancer attracted little attention.<sup>9-15</sup> Recent advances in the knowledge of lymphocyte function and interest in the relation of structure to function in the anatomy of the lymphoid tissue have called for a new look at the lymphoid tissue in humans.<sup>16,17</sup>

The present study based on 2250 axillary lymph nodes collected from 487 random autopsies is mainly intended to contribute to our knowledge of the appearance of the lymph nodes of one site of the body at autopsy. A detailed histopathologic study was not intended; rather, it was the purpose of our analysis to provide quantitative data concerning more general aspects of lymph node structure that could be obtained from a low-power microscopic survey. Histologic features selected for analysis include the germinal centers which are thymus independent, contain predominantly B lymphocytes and participate in humoral immune responses;<sup>18-22</sup> the deep cortical regions which are thymus dependent and participate in cell-mediated immune responses;<sup>23-29</sup> sinus histiocytosis, which has previously been described in cancer patients as a favorable prognostic sign;<sup>30,31</sup> hyaline deposits; fibrosis; and evidence of lymphocyte depletion. Each of the latter three has been described as a degenerative change denoting exhaustion of the immune function and response.<sup>32-37</sup>

## Material and Methods

The material of this study consists of 2250 axillary lymph nodes removed from 487 autopsies; 260 of these were performed at the Office of the Chief Medical Examiner, City of New York, during 1973 and 227 at the Pathology Department, University of Minnesota, during the years 1971 to 1973. In all cases, a piece of fat measuring up to 10 cm was removed from the axillary area and put in 10% formalin for fixation. The next working day the axillary fat was sliced and searched for lymph nodes by one of us (VT). The number of lymph nodes varied from 1 to 13, and usually 4 to 5 lymph nodes were found. The size of the lymph nodes varied from 0.2 to 4 cm. Each node was cut along the short axis and a central slice measuring approximately 2 mm in thickness was embedded in paraffin. From the paraffin blocks, one to four sections 5  $\mu$  thick were stained by hematoxylin and eosin. A routine histologic study of the lymph node sections was made, and for each autopsy case germinal centers, deep cortical regions, fibrosis, hyaline deposits, sinus histiocytosis and overall lymphocyte content were evaluated. Each histologic feature was recorded — when absent in all lymph nodes, + when present in a minimal degree, ++ when present in a moderate degree and +++ when present in a marked degree in any number of lymph nodes.

In grading the histologic features, criteria similar to those described by Cottier *et al*<sup>16</sup> were used. Lymphocytic follicles devoid of central, lightly stained areas were called germinal center —; those with central, lightly stained areas which under high-power examination failed to show any large lymphoid cells, tangible body

macrophages or mitoses were called germinal center +; those with central, lightly stained areas which showed lymphoid cells, tingible body macrophages and cells in mitosis were called germinal center ++; and those which were cytologically active and also large in size were called germinal center +++. Many of the latter showed rather irregular outlines and were fused. The deep cortical regions were marked — when the cortex of the node was generally thin and showed little “diffuse lymphoid tissue” between the lymphocytic follicles. Thicker cortices with appreciable amount of diffuse lymphoid tissue below the lymphocytic follicles were graded deep cortex +. Nodes with well-defined deep cortical regions often containing both large lymphoid cells and prominent endothelial cells in small vessels were recorded deep cortex ++. Deep cortical regions +++ were noted those nodes which were greatly expanded with resulting compression of both the outer cortex and medulla. Hyaline deposits were called + when observed only under high-power magnification. Such hyaline deposits were frequently associated with small blood vessels and reticular fibers of the cortex. Hyaline deposits ++ are those obvious under low magnification as forming small amorphous patches in the cortex. Hyaline deposits +++ were larger deposits of hyaline involving many areas of the cortex. Fibrosis was noted + when present in small amounts in the cortex around blood vessels. Larger amounts of fibrous tissue when confined in the lymphatic sinuses and medulla were called ++. When the fibrous tissue formed large bands obliterating the sinuses and involved portions of the cortical parenchyma, it was recorded +++. The overall lymphocyte content was noted as + when the lymph node appeared depleted of lymphocytes, as ++ when cellularity appeared “average” and as +++ when cellularity appeared markedly increased.

Eighty-five autopsies from Minnesota were performed by one of us (VT), and complete clinical and pathologic data were available. In the remaining 142 Minnesota autopsies, a copy of the face sheet of the autopsy report showing sex, age and race of the deceased as well as the main autopsy finding was obtained. The autopsy findings were classified in: a) lesions contributing directly to death, b) lesions resulting from or relating to a, c) significant lesions not related to a, and d) incidental findings. The University of Minnesota Hospitals is a general hospital, and only patients dying in the hospital are subject to autopsy. Only a few accident cases were admitted as prospective donors for kidney transplantation. Autopsies in Minnesota were performed soon after death, usually within the first 12 hours. The main clinical and pathologic findings from most of the New York cases were obtained during autopsy and in 80 cases the final autopsy report was reviewed. For some of the New York autopsies, little clinical information was available. In all cases at least the age of the deceased was known. As expected, accidents, homicides and suicides were among the leading causes of death in the New York autopsies. Many young adults and addicts were included in this group. In New York most of the autopsies were performed the day after death. Autopsies with significant autolytic changes were excluded.

Table 1 shows the total autopsy population in relation to source and age. The four arbitrarily chosen age groups are roughly related with the endocrine status which is known to affect the morphology of the lymphatic system. The first age group (16 years or younger) is the pediatric group and includes infants and children up to and around the age of puberty. The second group (17 to 39 years) includes young adults at sexual maturity. The third (40 to 59) comprises middle-aged adults in and around the menopause. The fourth (60 years or older) includes old, sexually inactive, individuals. As is shown in the table, children and the aged predominate in the Minnesota material and young adults and the middle-aged in the material from New York.

In this study the cause of death was generally classified in the following five

Table 1—Source of Material in Relation to Age

Source of material	Age group (yrs)				Total
	<16	17-39	40-59	>60	
University Hospital, Minnesota	63	40	48	76	227
NY Medical Examiner	20	123	74	43	260
Total	83	163	122	119	487

groups: a) death following external violence or acute illness (other than infectious), b) death due to acute infection, c) death due to chronic and acute drug poisoning, d) death due to cancer, and e) death due to other chronic diseases (diabetes, cirrhosis, collagen diseases, chronic heart and renal failure, etc).

## Results

Table 2 shows the incidence of lymph node histologic features in relation to age. Percentages indicate histologic features graded (++) or (+++), except for the lymphocyte content where the percentage indicates only (+++).

### Germinal Centers

As is shown in Table 2, prominent germinal centers were found in one fourth of the autopsies. Children showed the highest incidence (42.5%), old individuals the lowest (11.8%). In infants 3 months or younger the incidence was 18.6%. The latter group included 18 neonates, mostly premature. Eight infants, 1 to 2.5 months old, had germinal centers (Figure 1). (In 4 of them, the cause of death was reported crib death and 1 each died of pneumonia and heroin withdrawal syndrome.) Analysis of the 10 oldest individuals with germinal centers (70 to 85 years) showed that 3 died of acute infectious disease, 2 following car

Table 2—Incidence of Lymph Node Histologic Features in Relation to Age

Histologic feature	Age group					Total
	<3 mos	3 mos- 16 yrs	17-39	40-59	60+	
Germinal centers*	18.6%	42.5%	38.6%	16.4%	11.8%	25.0%
Deep cortex*	34.8%	15.0%	16.6%	1.6%	5.1%	9.6%
Hyaline deposits*	0%	7%	24.5%	53.4%	62.2%	37.4%
Fibrosis*	10.0%	27.9%	12.9%	23.4%	25.2%	19.7%
Sinus histiocytosis*	0%	4.8%	2.5%	2.5%	0%	1.7%
Lymphocyte content†	5.0%	4.6%	16.0%	5.7%	2.5%	8.2%

\* ++ or +++

† only +++

accident, 2 were cancer patients with death caused by pulmonary embolism, 1 died during heart surgery for coronary bypass, and 1 died of myocardial infarction. Table 3 shows the incidence of germinal centers in relation to the cause of death. As is seen in the table, persons dying following external violence, those with acute illness and drug addicts showed the highest incidence (34%) and cancer patients the lowest (3%). In patients dying of acute infections or chronic disease, the incidence was intermediate (9%).

#### Deep Cortical Regions

The incidence of expanded deep cortical regions was rather low (9.6%). It was highest in infants 3 months or younger (34.8%) and lowest in the middle-aged (1.6%). Several premature neonates exhibited lymphocytic deep cortical regions, sometimes without lymphocytic follicles whereas the rest of the node showed only hematopoietic cells. In infants the deep cortical regions were rich in post-capillary venules with high columnar endothelium. Among 241 individuals 40 years or older, expanded deep cortical regions were found in 8. Five died following external violence and 3 of acute infections (confluent bronchopneumonia).

#### Hyaline Deposits

Prominent hyaline deposits were found in more than one third of the autopsies. The incidence showed a highly significant relationship to age. It was 0% in infants, 7% in children, 24.5% in young adults, 53.3% in the middle-aged and 62.2% in the old. Of 40 children, 3 aged 14, 16, and 16 years, showed prominent hyaline deposits. Two died of reticulum cell sarcoma, one of external violence. Seven children, 5 years or older, showed minimal hyaline deposits (5 died of severe chronic disease, 2 following external violence). In 19 autopsies of individuals 60 years or older no hyaline deposits were found. Eight of these died of acute illness, 2 of cancer, 6 of other chronic disease and 3 following external violence.

Table 3—Incidence of Prominent Germinal Centers in Relation to Cause of Death

Cause of death	No. of cases	Percent with germinal centers
External violence, acute illness	122	34
Acute infection	25	8
Drug addiction	16	33
Chronic disease	31	10
Malignant disease	90	3

**Sinus Histiocytosis**

The incidence of sinus histiocytosis was minimal in all age groups (average 1.7%). In a total of 22 autopsies, sinus histiocytosis (+) to (++++) was found. Eight died of external violence, 5 of cancer, 4 of acute illness, 4 of drug addiction, and 1 of acute infection.

**Lymphocyte Content**

Increased lymphocyte content was found in 8.2% of autopsies. Incidence was highest in young adults (16%).

**Fibrosis**

Increased fibrosis was found in one fifth of autopsies. The incidence was not definitely related to age.

In Table 4 two groups of autopsies selected with criteria described elsewhere<sup>1,2</sup> are analyzed in relation to the cause of death. The first group, designated lymphocyte predominance, includes autopsies with lymphocyte content ++ or +++, hyaline — and fibrosis —; the second designated lymphocyte depletion includes autopsies with lymphocyte content ± or + and both hyaline and fibrosis being ++ or +++. As is seen in the table, the majority of cancer patients are found in the lymphocyte depletion group (96.2%). A smaller percent of patients dying of other chronic diseases is found in this group (67%). Deaths due to acute illness or drug addiction are mainly found in the lymphocyte predominance group.

**Other Findings**

During the course of our studies we observed that in patients who died of hemorrhage, the lymph nodes often showed lymphocyte depletion. The degree of depletion varied from node to node and case to case, but the deep cortical regions were primarily affected in most instances. In leukemic patients the last area to be involved with leukemic infil-

Table 4—Number of Cases in the Lymphocyte Predominance and Lymphocyte Depletion Histologic Groups in Relation to Cause of Death

Cause of death	Lymphocyte predominance	Lymphocyte depletion	Total
External violence	27	4	31
Acute illness	12	10	22
Drug addiction	18	6	24
Chronic disease	10	20	30
Malignant disease	2	51	53
Total	67	91	158

trates appeared to be the outer cortex. The depleted outer cortex stands out in sharp contrast with the heavily infiltrated remaining portion of the node. Similar involvement by abnormal cells was observed in one case of Gaucher's disease. Besides lymphomas and leukemias the most frequently observed metastatic cancers in the axilla were from the opposite breast in women and from prostate in men.

## Discussion

Our results show that human axillary lymph nodes undergo morphologic changes with age. In neonates the axillary nodes are rich in hematopoietic elements, *eg*, developing erythrocytes and granulocytes and deficient in lymphocytic elements. In these nodes, however, megakaryocytes were rarely found. Lymphocytes are mainly found in lymphocytic follicles and/or the deep cortical regions. Examples of lymph nodes showing lymphocytic follicles without lymphocytic deep cortical regions and vice versa were found. Thus it is not clear from this study which of the two areas develops first in human ontogeny. Examination of fetal lymph nodes may clarify the question. Ehrlich<sup>4-6</sup> found that both lymphocytic follicles and deep cortical regions develop during fetal life; he believed that the deep cortical regions (which he called tertiary nodules and pseudonodules) derived from expansion and fusion of lymphocytic follicles during the immune response, but this seems unlikely in view of the cellular composition of the two areas (B cells in lymphocytic follicles, T cells in deep cortex). Silverstein and Lukes<sup>14</sup> did not find evidence of cortical differentiation in the lymph nodes of 5 fetuses. These authors described five stages of lymph node morphologic maturation: stage I—unorganized aggregates of lymphocytes with a definite capsule, II—development of medulla, III—differentiation of medulla and cortex with lymphocytic follicles, IV—early germinal centers in cortex, and V—further increase in number, size and activity of germinal centers. In this classification, the appearance of deep cortical regions should be included in stage III. In neonates the lymph nodes regularly showed wide sinuses and what appeared to be medullary cords without definite cortex. The cortex first appeared as nodular collection of lymphatic tissue beneath the subcapsular sinus. These lymph nodes showed rich vascular supply with many postcapillary venules exhibiting high columnar endothelium (Figures 2 and 3). In some cases the only lymphocytes present in the node were found around the postcapillary venules. This finding supports previous reports on the significance of postcapillary venules in recirculation of lymphocytes and the development of deep cortical regions.<sup>38-44</sup>

Germinal centers are the most extensively studied histologic feature of the lymphoid system. Although no quantitative studies have been made, it is generally agreed that germinal centers first appear some time after birth, within the second or third month. They are prominent in children and young animals and, in the absence of chronic inflammation, rare in the old.<sup>6-8,45-49</sup> In our material germinal centers first appeared in 2 infants, both 1 month old. Prominent germinal centers were found in approximately 40% of children and young adults. In older individuals, germinal centers were less frequently found (14%), but they persisted until advanced senescence. The incidence was high (34%) in patients dying following external violence, acute illness or drug poisoning and low (3%) in patients dying of cancer. In those dying of acute or chronic infection, the frequency was rather low (8 and 10% respectively). In contrast, Black and DeChabon<sup>50</sup> found that in patients dying following trauma or acute illness or azotemia germinal centers were "uncommon" in the axillary lymph nodes.

In drug addicts, the lymph nodes have been found to be large and "hyperplastic"<sup>13,51</sup>; we found a high frequency of germinal centers in such nodes. Nelson and Hall<sup>15</sup> reported decreased numbers of germinal centers in the pelvic lymph nodes of women in pregnancy and complete disappearance of germinal centers at term. Of four autopsies of women whom we studied in the puerperium, 3 showed prominent germinal centers in their axillary lymph nodes. A fourth showed lymphocyte depletion associated with extensive hyaline deposits (a massive hepatocellular carcinoma with metastases was found at autopsy). Experimental studies have shown that germinal centers appear regularly 4 to 12 days following antigenic stimulation.<sup>53</sup> Thus the relatively low incidence of germinal centers in patients dying of acute or chronic inflammatory disease may appear contradictory. In this connection it might be important to consider that the impact of a fatal infection on the immune system might be quite different from the impact of a disease with a more or less benign course. Along these lines, discrepancies in the morphology of axillary lymph nodes between surgical material and autopsy material may be explained. In a previous study<sup>2</sup> the morphology of the axillary lymph nodes from mastectomy specimens of patients operated for breast carcinoma was classified in lymphocyte predominance (54%), germinal center predominance (17%), unstimulated (25%) and lymphocyte depletion (14%). In the present study 96.2% of cancer patients showed lymphocyte depletion, only 3% showed prominent germinal centers, and none showed lymphocyte predominance.

In contrast to germinal centers very few studies<sup>4-6</sup> on the morphology

of the deep cortical regions were made until recently when their significance in cell-mediated reaction was recognized.<sup>23-28</sup> Prominent deep cortical regions were found in approximately 10% of autopsies. Along with the germinal centers, they were more frequent in children and young adults than in the old. The same frequency of expanded deep cortical regions was found by Turk and Oort<sup>28</sup> in a large series of "normal" human lymph nodes obtained from surgical specimens. We found much higher incidence in radical mastectomy specimens.<sup>2</sup> Sinus histiocytosis was observed in less than 2% of autopsies. No evidence of spontaneous infarction,<sup>54</sup> heterotopic epithelium<sup>55</sup> or granulomas were found in this study.

Among the degenerative changes, hyaline deposition was definitely related to age. Fibrosis and lymphocyte depletion were related to the cause of death rather than age. Combination of lymphocyte depletion, fibrosis and hyaline deposition was found in over 90% of cancer patients. While most cancer patients received radiotherapy and other immunosuppressive agents which may produce lymphocyte depletion and fibrosis in at least three patients, there was no treatment at all and diagnosis of cancer was made postmortem. It is our experience that marked lymphocyte depletion associated with fibrosis and extensive hyaline deposits is characteristic of lymph nodes of patients dying of cancer (Figure 4). Patients with other chronic diseases, for example, systemic lupus erythematosus, systemic scleroderma and rheumatoid arthritis, who also are often treated with immunosuppressive drugs show enlargement of lymph nodes associated with lymphocyte predominance. In this study, as in others,<sup>56,57</sup> lymphocyte depletion was usually associated with marked increase in the number of plasma cells.

The depletion observed in patients who died of hemorrhage is different from that observed in shock<sup>58</sup> because it affects primarily the deep cortical regions. Similar depletion was observed in mice following thoracic duct drainage<sup>59</sup> and the calf after extracorporeal irradiation of blood.<sup>60</sup> Selective depletion of the deep cortical regions associated with death from hemorrhage may be due to a more rapid recirculation of T rather than B-cells,<sup>57</sup> and thus represent depletion of a readily mobilizable lymphocyte pool.

In conclusion, this study on the histologic appearance of human axillary lymph nodes at autopsy has: a) presented quantitative data supporting the general opinion that germinal centers are more frequently found in children and young adults than in the old, b) showed that hyaline deposits increase with age, c) showed that lymphocyte depletion associated with fibrosis and hyaline deposits was found in

patients dying of chronic disease, particularly cancer, d) pointed out a selective depletion of the deep cortical regions in patients dying of hemorrhage, and e) has contributed to knowledge of the morphology of axillary lymph nodes in neonates.

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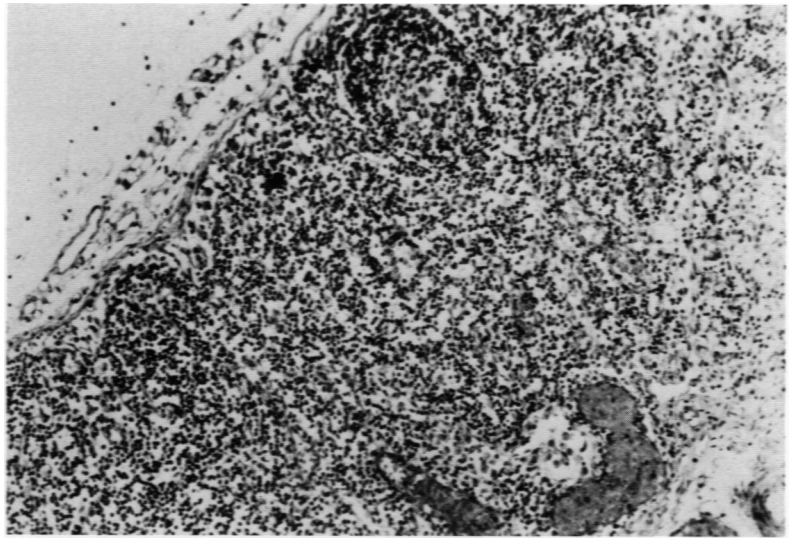
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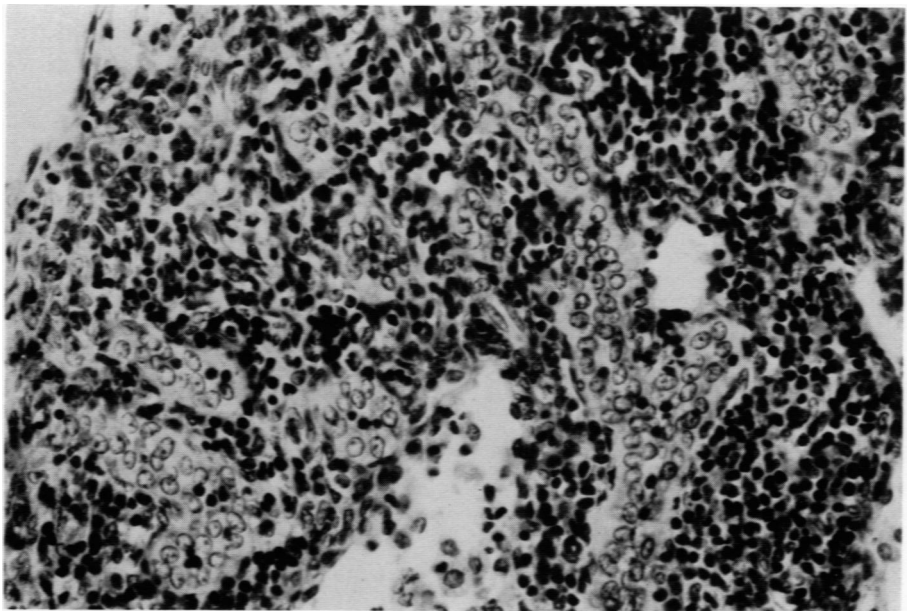
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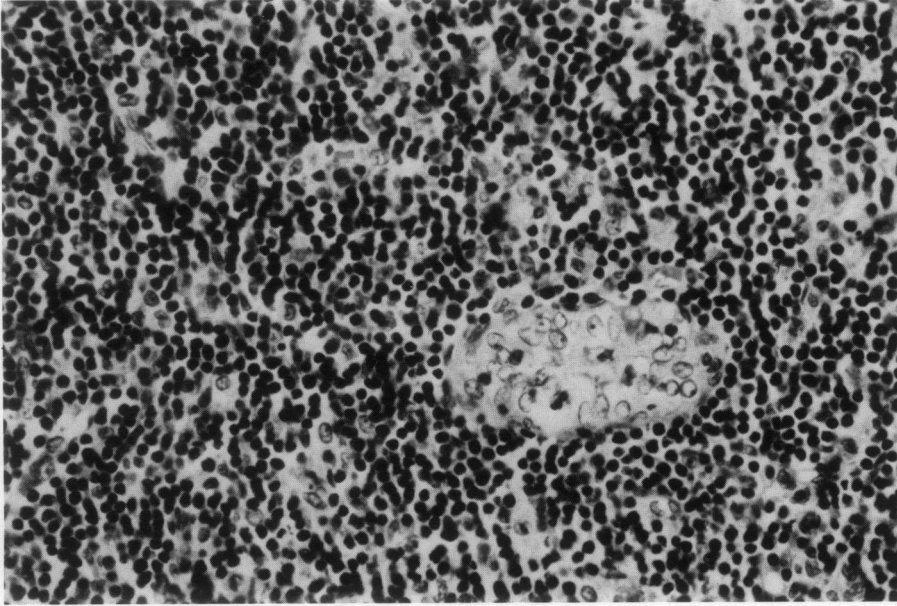
*[Illustrations follow]*



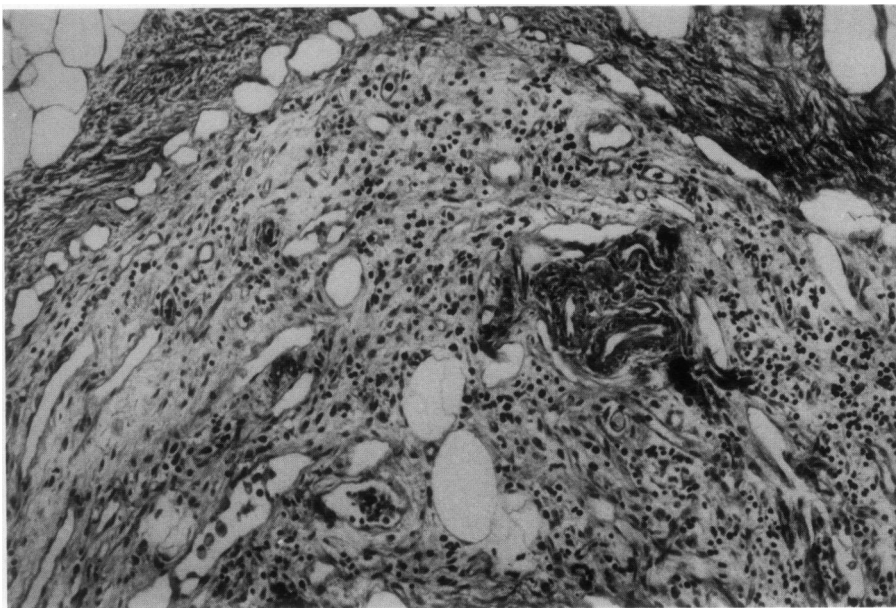
**Fig 1**—Germinal center in outer cortex. Two-month-old infant with sudden unexplained death (H&E,  $\times 63$ ).



**Fig 2**—Developing lymph node cortex rich in blood vessels with prominent endothelial cells and poor in lymphocytic elements (H&E,  $\times 250$ ).



**Fig 3**—A venule in the deep cortex shows prominent high columnar endothelium (H&E,  $\times 250$ ).



**Fig 4**—A lymph node from a 32-year-old male with Hodgkin's disease, stage IV, showing extreme lymphocyte depletion (H&E,  $\times 63$ ).